Acceptability of generic versus innovator oral medicines: not only a matter of taste

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Title

Acceptability of Generic vs. Innovator Oral Medicines: Not Only a Matter of Taste

Short Title

What would make Generic medicines better?

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Conflict of Interest Statement

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Key words

Generic; Acceptability; Palatability; Swallowability; Appearance; Cost effectiveness

Teaser

Reduced patient acceptability of generic products, especially oral ones, can undermine adherence and clinical effectiveness and hence compromise their potential benefits.

Research highlights

Lack of formal scrutiny of the acceptability of generics may reduce patient adherence.

Abstract

Optimum use of generic products would require equivalence, not only in terms of quality, safety and efficacy in clinical studies, but also patient acceptability in order not to jeopardize treatment success due to non-adherence which would de facto limit the potential cost saving anticipated by their use. Although acceptability is a requirement for the authorisation of paediatric innovator products, our survey of EU regulatory authorities uncovered that few have a formal process for assessing patient acceptability of generic products during the registration processes. The current International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use focus on unifying guidance for the development and scrutiny of generics should include acceptability alongside the other factors being considered for harmonization.

Introduction

Once a medicine is no longer under patent protection and the period of market exclusivity has expired it is likely that a generic version will become available. The lower acquisition cost of generic medicines is a strong incentive for prescribers, pharmacists and health care systems to use them in preference to the innovator product, all other factors being equal. Indeed, in some jurisdictions there is financial pressure on prescribers and pharmacists to supply the cheapest licensed product available. In others, generic substitution, even when a product is prescribed by brand name, is encouraged or even mandated [1]. In England, for instance, 84% of all drugs in primary care are prescribed generically, potentially generating significant savings for the National Health Service (NHS) [2].

In France pharmacists must provide a generic product even if the prescription is written by proprietary brand name. The prescriber can only object to this substitution in the following three circumstances. Firstly, if the medicine has a "narrow therapeutic index" (NTI) such as levothyroxine, phenytoin or theophylline and the patient is already effectively stabilized with a particular brand. Secondly, for children less than 6 years of age, if there is no generic drug in an age-appropriate dosage form available. And finally, the original medicine may be prescribed if it does not include an excipient, present in all available generic medicines, to which patients have a demonstrated contraindication [3]. If these conditions are not met and the branded product is supplied, the reimbursement process can become quite complex for the patient [4].

If all generic products were equally as acceptable as the original product this would be less of an issue. However, this is not always the case.

The purpose of this paper is to explore more formally the level of scrutiny of the acceptability aspects of generic product development and to highlight the added value of generics if non inferiority is achieved in terms of acceptability as well as bioequivalence (BE). We discuss the findings of a purposive literature review of the relative palatability of generic products and corresponding impacts on medication adherence. We also present the findings of a survey of a number of regulatory authorities, to establish whether the relative acceptability of generic products is one of the factors that are considered as part of marketing authorisation. The outcomes of the review and the implications for product development are discussed.

Although this paper focusses largely on oral medication, as the most commonly used mode of administration, the topics addressed are applicable to all product types, though each has their own critical acceptability criteria and challenges.

Given the expertise of the authors and the critical part that acceptability plays in paediatric medicine use, this paper focuses mainly on this patient group. However, the main points are also applicable to some extent to all medicine users and in particular to other vulnerable patient groups such as the elderly and those with particular formulation needs such as those who experience swallowing difficulties and those with cognitive issues [5,6]. We have included occasional references to these groups where they serve to illustrate a particular point. Since the focus of the paper is mainly on oral paediatric medicines many of the examples given are for antibiotic formulations since they are a class of medicines frequently prescribed for children [7,8] and they often have challenging organoleptic characteristics. These are illustrative of the issue as a whole.

Potential advantages of Generic products

Generic products may offer several advantages over their innovator counterparts, not least in relation to costs. A product that is normally a tablet may be easier to swallow; while a capsule can improve ease of administration for patients who need to mix the medication with food or disperse in water and administer via an enteral tube. As another example, a liquid dosage form of a product which is usually a tablet may aid dose measurement.

The packaging is also unlikely to be exactly the same, potentially offering scope to provide a product which the patient would prefer to handle or which is easier to differentiate from other medicines.

Finally, there may also be scope for improving continuity of supply if generic products are available from several different manufacturers. However, the counter to this is that if there are several generics available, different products may be supplied on different occasions with implications that are discussed below.

Where such benefits arise, the mechanism and logistics of specifying a particular generic for supply to the patient and issues around reimbursement are likely to be problematic for the patient, prescriber and dispensing pharmacist. For example, there is currently no formal mechanism for allowing a doctor to prescribe a particular generic or for the pharmacist to supply one from a particular supplier and to obtain reimbursement above and beyond the reference price should that particular generic be more expensive. Even where the pharmacist does choose the generic product that will be stocked in their pharmacy it is unlikely to be economically viable to stock multiple versions.

Although a specific generic could have enhanced acceptability to a particular patient relative to the innovator product, experience and literature reports suggest that the opposite is more likely the case [9,10]. A lack of consideration of the acceptability of generic products could undermine the potential

considerable cost saving and other advantages that could be achieved by promoting their use. As with all medicines, it may be possible (but by no means certain) that acceptability could be improved by patient/provider education. However, this is highly unlikely to be particularly effective for young children, the main focus of this paper, or for elderly patients with cognitive or functional impairments.

Bioequivalence Considerations

Generic products must be bioequivalent with the innovator or receive a waiver, for example, based on the Biopharmaceutical Classification System (BCS) class of the Active Pharmaceutical Ingredient (API) or meeting specified requirements for certain dosage forms or products [11-13]. To be bioequivalent, a suitable pharmacokinetic (PK) study (such as a randomised crossover or parallel design) in healthy volunteers needs to show, for both peak drug concentration (Cmax) and area under the curve, that the 90% confidence interval of the ratios (generic : reference) lie between 0.80 and 1.25 [11]. To meet this requirement the variation in PK parameters between the generic and the reference is actually small [14], but nonetheless may have important implications, especially for medicines with a low therapeutic index (TI). In these cases, the BE requirements are tighter (0.90 to 1.11) and Cmax control may also be required. However, differences in acceptability between both products could have a detrimental effect on adherence, as very simply, “drugs don’t work in patients who don’t take them” [15].

It is important in this context to remember that BE studies are generally performed in adults in controlled environments even for paediatric formulations when it will be children that actually take (or do not take) them in a domestic setting.

Acceptability Considerations

Currently, legislation and regulation-related guidance from the United States (US) Food and Drug Administration (FDA) and the European Medicines Agency (EMA) mandate development of formulations for children concurrently to those for new “innovator” products for adults. Among other criteria, the acceptability of the formulation itself needs to be demonstrated [16]. As per EMA definition, acceptability is an overall ability of the patient and caregiver (defined as “user”) to use a medicinal product as intended (or authorised) [17].

Acceptability of a medicinal product is likely to have a significant impact on the patient’s adherence and consequently is likely to have an impact on the translation of a product’s into clinical effectiveness (that is, the performance of a medicine when used in the context of routine care) [18,19]. It is driven by the characteristics of the user (e.g. age, individual health status, behaviour, disabilities, background

and culture, prior expectations) and by the characteristics of a medicinal product. For example, for oral dosage forms, these would be:

- Palatability; (e.g. taste, flavour, sweetener, mouth feeling, product texture);
- Swallowability (e.g. size, shape, "stickiness", integrity of dosage form, film-coating);
- Appearance (e.g. colour, size, shape, embossing);
- Complexity of modification prior to administration (if required);
- Required dose (e.g. the dosing volume, number of dose units, scoring);
- Required dosing frequency and duration of treatment;
- Selected administration device (if any);
- Primary and secondary container closure system;
- How the dosage form is to be taken and how often it is to be administered.

Anecdotal evidence suggests that generic products (and in particular oral liquid dosage forms often used in paediatrics) may not/do not receive the same level of regulatory scrutiny as do innovator products in terms of their acceptability. Although not always the case, this can lead to generic products being approved with poorer acceptability, which in turn can influence their clinical- and cost-effectiveness via reduced adherence [20] as discussed.

The lack of scrutiny of acceptability factors does not only affect paediatric medicines. The situation is no better in the context of polypharmacy in older people, where patient-centric drug design should, but does not always, consider their needs, ability and preferences. It is crucial to consider administration-related factors (e.g. difficulty in swallowing, handling and palatability) to ensure that efficacious treatments in clinical trials are effective in practice. As an example size is an important acceptability driver for older patients [5]. Similarly taste masking should not be neglected for older patients even if it is often thought that older people are less sensitive to palatability issues [21].

Thus acceptability factors should be considered when assessing the suitability of particular formulations in meeting patients' needs no matter what their age.

A further aspect that should perhaps be considered when developing any medicine and, in the context of this paper, generic versions of innovator products, is their pharmaceutical elegance (those aspects of the product that the patient perceives as indicating its quality) and the expectations that this may produce within the patient. There is a corpus of literature concerning the interaction between patients' expectations produced by the packaging, the product, the environment and their prior experiences, on their subsequent perception of the acceptability of the final product and hence the likelihood that they will take it as intended. Extensive discussion of this aspect is beyond the scope of this current paper but a few references are given to illustrate the concept [22,23].

If there are multiple generic versions of a product available, then although some generics are formulated to match (as far as possible) the appearance and properties of the innovator product, this is not universally the case as they will be approved regardless, provided the product complies with all required standards of quality, safety and efficacy. Even if the individual generic products are acceptable in their own right they can still differ significantly both from the innovator and each other including the possibility to differ in pharmaceutical form (e.g. tablet versus capsule, tablets of different size, shape and colour etc). Given the supposed interchangeability of (generic) drugs, it is entirely possible for a different formulation to be supplied on different occasions (or between different pharmacies). This can lead to frequent changes to the type, appearance, storage, dosing, administration requirements [24]; or organoleptic properties of medicines dispensed to the individual, which may lead to confusion and present a further barrier to adherence. There is an additional risk of medication error, should the patient take more than one formulation of the same API at the same time with obvious therapeutic and toxicological sequalae.

What actually happens in practice?

To explore the issues concerning the acceptability of genetic medicines, we conducted a purposive literature review that focused mainly on paediatric populations; and conducted a survey of European regulatory authorities' approaches to assessing the acceptability of generic medicines during their marketing authorisation review. We also present our understanding of the regulatory situation outside Europe.

a) Purposive review

A search was performed in PubMed up until June 2019 using the search terms: (acceptability OR palatability OR taste) AND (drugs; generic OR drugs; non-proprietary) in order to identify publications that discuss the relative acceptability of innovator and generic versions of medicines. Therapeutic areas where acceptability issues are known to be a significant in paediatrics were also investigated namely anti-bacterial agents OR corticosteroid as exemplars of the issues discussed. These categories cover the most frequently prescribed oral medicines in children. Asthma treatments are not considered as these tend to be delivered via the pulmonary route.

In addition, some publications highlighting the impact of formulation and presentation changes on the acceptability of an API were identified from a broad personal database—updated since 2014—which gather papers on medicine acceptability in vulnerable populations. Herein we discuss 24 key

references that had a direct relevance to this paper. Table 1 lists those key references and provides reasons for the few not discussed.

Table 1

Many studies have demonstrated differences in palatability between distinct formulations of an API. As early as 1984, differences in children's taste ratings were demonstrated among three different oral suspensions of bacampicillin as well as two penicillin syrups [25]. Two years later, Uhari et al [26] similarly highlighted acceptability differences for penicillin and erythromycin mixtures—varying in terms of sweeteners and flavours. Indeed, an erythromycin mixture, flavoured with cherry/sodium-citrate was significantly better than the mixture flavoured with pineapple/menthol, both on the basis of the time required to give the medicine to the child (as recorded by the nurse), and the subjective score of drug acceptance given by the nurses. Such acceptability variation due to flavour were also observed for pivampicillin mixtures [27] and ondansetron syrups [28].

A study of US-approved antibiotic suspensions highlighted that the generics were rated lower or equal in taste to the respective innovator products [9,10]. The originator product tasted better than the generic product for trimethoprim-sulfamethoxazole, while there was no taste difference in relation to cephalexin and erythromycin-sulfisoxazole suspensions [10]. It is not clear in the latter case whether this was because all formulations were equally acceptable or equally unacceptable. Similar findings were observed for the acceptability of antibiotics approved in France [29,30]. While there was no significant difference between amoxicillin innovator and generic products, differences in palatability and acceptability between Augmentin and other co-amoxiclav products appeared significant [29,30]. These findings underlay a specific problem of oral generic antibiotic drugs, that is, of their acceptability to children and hence adherence to treatment courses [31-33]. Differences among reference and generic products have also been highlighted for other therapeutic contexts, such as corticosteroids which are frequently related to poor taste [34]. Although these results were based on human testing (e.g. child's evaluation, observer reports), innovator and generic formulations could be also distinguished using biomimetic taste sensing systems [35]. These instrumental results were often correlated with those from gustatory sensation tests performed by well-trained adult volunteers [36-38].

In paediatrics, differences in acceptability between innovator and generic products appeared to be mainly due to taste and this in turn can be influenced by age. Bagger-Sjoback and Bondesson showed in 1989 that taste differences could be driven by age of patient: two paediatric formulations of phenoxymethylpenicillin were differentiated by grade-schoolers (from 6 to 10 year) but less so by pre-schoolers (from 3 to 5 years) [39].

Other aspects identified in the search that had an influence on overall acceptability that differ between generics and innovator products in children include administration devices [40] and physical attributes such as size of solid dosage oral form [41].

Similarly, taste issues have often been overlooked in the elderly, another vulnerable population. Recent studies using a multivariable approach initially developed for paediatrics [42,43] then transposed for the older population [44], have highlighted that taste/palatability remains crucial for the acceptability and therefore correct use of oral liquid pharmaceutical products, especially in older women [6,21]. As for paediatric patients, studies of many aspects of a medicine's characteristics are needed to better understand overall acceptability, from taste to administration device [40] or physical attributes such as size of solid dosage oral form [41].

Even for solid dosage forms where taste is less of an issue, the name, packaging, appearance, size, shape or pharmaceutical form (i.e. tablet or capsule) could cause confusion for some patients [45]. Acceptability could also be affected by swallowability [45]. The potential for confusion, along with variability of presentations, were raised as the main disadvantages of generic products by general practitioners, who suggested that drug composition and packaging could be made uniform to mitigate some of the drawbacks associated with generics while taking advantage of their lower cost [46]. A recent cohort study supported this conclusion [47]. Based on more than 200,000 cases in the US, researchers highlighted that switching to a generic identical in composition and appearance to the innovator drug product was associated with lower switchback rates compared with switching to generic drug products that were different to the innovator [47]. Although low, there was still a degree of switchback from the "identical" generic to the innovator product.

Although generic medicines have the same API as the innovator product and must be bioequivalent and of equal quality, they may differ in term of excipients and consequently in taste/palatability.

For paediatric products, innovator products have to be tested to confirm acceptability during product development [17] since it is widely accepted that medicine acceptability could impact effectiveness. In theory, an "identical generic" could be assumed to have identical acceptability to that of the innovator product. However, producing a generic that is truly identical may prove to be a significant challenge. For example, sourcing exactly the same flavours may be problematic and simply using similar ones may lead to significant organoleptic differences either initially or over the shelf life of the product as the flavour ages.

If a generic is not identical in all respects to the innovator drug product, the same acceptability testing as that required for the innovator, should be considered by regulatory authorities. As will be discussed in the next section, this may not always be the case.

Unacceptable medicines can impede the benefits of even the most effective drug, yet many parents and other carers are faced with the daily challenge of getting their children to take their treatments. "I don't like the taste" remains the number one challenge for children in taking medicines (over 60% of 652 respondents in a recent survey) [48].

b) Approach taken by European Regulatory Authorities

To understand the current position of various regulatory authorities as regards to their requirements for acceptability testing of generic formulations, 31 national European Union (EU) regulatory agencies were emailed, either via personal contacts or via the EMA paediatric committee (PDCO) list, during the summer of 2019 [49]. The project was introduced, and the following questions were asked.

- Does your country allow marketing approval of generics of different oral dosage forms to that of the innovator product?
- Do some formal or informal discussions take place regarding acceptability of generic *vs* originator medicines?
- What relevant regulatory documentation does your country use when considering this area?

Responses were received from 14 (45%) regulatory agencies. Belgium, Croatia, Denmark, Estonia, Greece, Iceland, Ireland, Latvia, Netherlands, Slovakia, Slovenia, Spain, Sweden, UK all answered that they allow marketing approval of generics of different oral dosage forms, if the conditions of Article 10 of the Directive 2001/83/EC are fulfilled [50].

The responses varied from the very detailed to the very brief but were sufficient to provide a good level of understanding of the situation in Europe. As presented in table 1, only three respondents (from UK, The Netherlands and Croatia) affirm that there was some level of formal scrutiny around acceptability of generic vs originator medicines at least for paediatric submissions. Based on anecdotal data it is probable that informal discussion of these aspects may be more widespread, particularly in terms of tablet dimensions and shape. However, it appears that discussion about the choice of flavouring is less common and formal requests for data on these aspects are rare.

Table 2

Surprisingly only 3 agencies report that they routinely formally consider acceptability when evaluating generic products given that differences between generic products and their originators products should be considered as part of the Risk Management Plan (RMP), as detailed in the EMA position paper on "Potential medication errors in the context of benefit risk balance and risk

minimisation measures" [51]. This concludes that "If a product containing the same active substance as an authorised/established one, but which is different in some aspects, including new indications, patient populations etc., is developed, the potential for medication errors caused by confusion with the authorised/established product, should be considered in the development and presentation of the product.". The guidance does not specifically reference acceptability, but perhaps it should do so.

It appears that the risk of administration errors has been more formally recognised in the case of formulations for the elderly [52]. This reflection paper recognises that patients "commonly recognise oral preparations by their size, shape, colour, embossing, rather than by reading the product label, whereas preparations for other routes of administration may be recognized by their immediate container closure system", and that even carers, whether in the home or in an institutional setting, "are also likely to administer medicinal products to the mainly older patients by a visual verification of the product appearance". It acknowledges that confusion based on these factors and changes in them can lead to medication errors. Innovators are therefore encouraged to ensure that they "carefully compare the appearance and user instruction of their own product versus others on the market (e.g. sound or lookalikes)" and where relevant, to introduce "appropriate measures in the product characteristics such as the formulation, packaging or product information" to mitigate risk. Given the highlighted issues we encourage generic manufacturers to also ensure their products "have the same key visual appearance (i.e. colour, size etc.) and user instruction" as that of the originator product; the latter should be up to date and address older people's specific needs. As we point out elsewhere in the paper although this is highly desirable guidance it is not mandatory and not always applied in practice.

Regulatory landscape outside Europe

Our survey confirms that in the EU, competent drug regulatory authorities may allow a generic drug and its reference product to be different oral dosage forms if the product meets bioequivalence criteria. In the US this is not the case. The FDA does not allow a generic drug and its reference product to be different oral dosage forms (e.g. tablets and capsules). In fact, the FDA guidance on "Size, Shape and other physical attributes of generic tablets and capsules" [41] recommends generic oral tablets and capsules to be of similar shape and size to the reference product (brand leader or originator product). "Similar" can be interpreted as not identical allowing some increase in dimensions and weight. However, this guidance does not mention testing of acceptability. There is also an earlier FDA guidance on "Size of Beads in Drug Products Labeled for Sprinkle" [53]. This provides guidance on the maximum, but not minimum size of granules to be used in such "sprinkle" products to avoid them being chewed and applies to all such formulations. However, there is no requirement for either the

formulation or the granule size to be the same for generics and the innovator product with clear potential for the organoleptic acceptability to differ. This may be more important if such products are administered via a nasogastric tube.

Our review is based on a Western developed world perspective. Whilst many other territories follow either European or US regulatory standards and guidance, this is not always the case. It was outside of the scope of this review to locate specific relevant guidance on the evaluation of the acceptability of generics in significant markets such as China, Africa, India and emerging markets. However, it seems likely that a lack of the scrutiny of acceptability of generics also applies in these markets. Given issues of access and cost generic acceptability may be even more important in these territories than in Europe and the USA.

Why does all this matter in clinical practice?

Generic medicines are licensed in the EU in line with the requirements of Directive 2001/83/EC as amended [50]. Article 10 of the directive provides for 3 main categories of "generic" where a change of pharmaceutical form may result.

- 10(1) a "true" generic medicinal product;
- 10(3) a hybrid application;
- 10(a) well established use (not actually a generic application, rather a formal recognition of medicines with a long and safe history of use).

EU countries that allow marketing approval of generics base their assessment on bioequivalence of the generic to the innovator with acceptability playing a significantly lesser role at present. Although "a generic medicinal product" is defined as "a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies", article 10.1 goes on to state that "the various immediate-release oral pharmaceutical forms include tablets, capsules, oral solutions and suspensions, are considered to be the same pharmaceutical form for the purposes of Article 10." This is also reflected in the Notice to Applicants (2A, chapter 1, section 5.3.2.1) and the Bioequivalence guideline [11].

As a consequence, there is no requirement for generic medicines to be the same colour, shape, size, etc. or to bear the same embossing as the reference product. Nor does the pharmaceutical form need to be the same. A generic tablet (article 10.1) referencing a capsule, or oral suspension, or oral

solution originator (or vice versa) would be acceptable and could obtain a marketing authorisation provided all other requirements are met.

More changes are allowed in other article 10 applications. Some recent examples serve to illustrate the point:

- A 10.3 hybrid application for hydrocortisone granules in capsules for opening (Alkindi®) referring to hydrocortisone tablets [54]. The main differences in Alkindi® compared to the reference medicinal product are: change in pharmaceutical form; change in strength; indication in replacement therapy in paediatric patients only.
- A 10.3 hybrid application for an orphan drug indication for mercaptopurine in treatment of lymphoblastic leukemia. The generic oral suspension formulation references Puri-Nethol tablets [55].
- Sialanar® is an oral liquid dosage form containing glycopyrronium and is a 10a well established use (WEU) application. Glycopyrronium has been licensed for many years. Prior to Sialanar® oral liquid there were injections and solid dosage forms licensed. The Sialanar® WEU application has resulted in new indications and a new dosage form for this drug substance [56].

The implications of this presumption of equivalence and hence presumed "substitutability" between various immediate release formulations is clearly not necessarily true in terms of acceptability.

What are the product development implications?

Based on the aforementioned published findings in the literature and information provided by the responses to the survey, it is possible to provide some detailed discussion for each of the individual factors that influence overall acceptability.

Palatability

At least some regulators are aware of the literature showing potentially significant differences between formulations, for instance one quoted the study referred to above which found that several brands of generic co-Amoxiclav tasted worse than the innovator (Augmentin) [29]. This study, which acknowledged financial support from the former French medicines agency (Afsaaps until 2012), called for the evaluation of palatability of future drugs (generics and references) before granting of the marketing authorization, since particularly for active substances of poor taste, palatability plays a significant role in adherence to the treatment, especially in children.

It is also acknowledged that other antibiotics also pose palatability challenges [33]. For example Floxapen®, the brand leader formulation of flucloxacillin has very poor palatability. Anecdotally, many generic flucloxacillin brands are equally unpleasant. This issue of poor palatability is highlighted in some hospital formularies. For example, the formulary of Evelina Children's Hospital, London, states: "Fucloxacillin liquid is not very palatable" [57]. The impact on adherence of unpalatable antibiotics is discussed on forums such as Mums Net and acknowledged internationally (e.g. pharmacists in Canada have suggested tips for giving antibiotics to children [58]).

A recent example that is a good illustration of the need for generics to have acceptable palatability concerns two new licensed omeprazole products (two strengths). Although the manufacturer intended this solution formulation to be used for administration via use with enteral tubes, as it is the only licensed formulation, it is being prescribed for oral use in the community. However, the Neonatal and Paediatric Pharmacists Group (NPPG) blog reported recently [59] that "*children don't like it saying that it does not taste nice and 'burns'*." Some consider it "*utterly revolting*" and cases of emesis following swallowing of the dose have been reported. Some children have asked to go back to their old (unlicensed) liquid formulation.

In spite of the known issues of poor palatability of legacy, and some new, products some survey respondents were not aware of a major objection preventing the marketing of a product on the basis of poor palatability having ever been raised. However, our survey reported one instance (personal communication) where a generic oral liquid product that was formulated at a higher concentration than the originator, presumably in order to reduce the dose volumes, and which the applicant originally proposed for use in both children and adults, was restricted to use in adults only as palatability was demonstrated to be worse than the more dilute reference product [60].

Poorly acceptable legacy products rely on voluntary reformulation by the marketing authorisation holder (MAH) as there is currently no regulatory instrument that would support a request for reformulation. The paediatric-use marketing authorisation (PUMA) procedures have not incentivised alternative taste masked dosage forms.

Modern regulatory procedures such as paediatric investigation plans (PIPs) along with such regulatory guidance as EMA guideline on paediatric development pharmaceutics, and their requirements for age appropriate, acceptable, formulations will prevent unpalatable *innovator* medicines for children in the future and force development of alternative formulations if taste cannot be masked. For innovator products, acceptability/palatability studies will be performed as part of product development, probably as part of the clinical studies which companies will need to undertake in any case. However, performing such studies in patients may not always be a requirement for

generic product developers. If the API/product is BCS class I or III or an oral solution then they may not even need to undertake a bioequivalence study and thus will have no obligation (nor opportunity) to demonstrate the palatability of the product. If they do undertake bioequivalence studies there is no requirement to include palatability assessment as part of those studies, and even if palatability studies are conducted the data will be generated in adults rather than children or the elderly. Including taste studies will of course increase the cost. Thus, the level of scrutiny applied to innovator and generic versions of those products is very different.

Perhaps the subjectivity of taste and lack of defined methodology may contribute to regulatory uncertainty in this area. A range of possible methodologies have been proposed and various groups including the European Paediatric Formulation Initiative (EuPFI), IQ Consortium and some regulators have begun discussions on identifying and agreeing unified methodologies for assessing the palatability and overall acceptability of pharmaceutical products but these efforts have yet to bear fruit.

Swallowability

Solid oral dosage forms (SODF) are being used increasingly for children. The "Guideline on pharmaceutical development of medicines for paediatric use" [17] states that "The size and shape of a tablet are fundamental to the ability of a child to swallow it. Therefore, the acceptability of the size and shape of tablets by the target age group(s) should be justified, and where relevant supported by appropriate studies or clinical evidence". Generic versions of a solid dosage form may be a different shape or size and so could be less acceptable especially if they are physically larger, or appear to be so. This might be especially so if one product is a capsule whilst the other is a tablet and this will cause difficulties in generic substitution.

As it is currently permissible at least in Europe for a generic to be a different pharmaceutical form to that of the innovator, swallowability might be improved by changing from a solid oral dosage form to a liquid. However, taste issues may then be made worse and aspects such as portability and dose measurement may need to be considered. It is not yet clear whether the risk of medication error is increased or reduced in such cases, and this will likely vary on a case by case basis.

Appearance

Enhanced acceptability has been suggested as one reason for inclusion of colours in medicines, especially for children. The inclusion of colour either on packaging or in the dosage form itself may also be employed to help differentiate strengths.

Differences in colour may exist between innovator and generics products (and among different generics), in some cases, particularly over-the-counter (OTC) medicines, the same basic formulation may exist as either a coloured or colour-free presentation. Although there is some evidence that adherence with prescribed therapy can be influenced by colour [61], there is a clear risk that differences in appearance (including form, size, shape, embossing and colour) could lead to elevated risks of medication errors. These include selecting the wrong product at the pharmacy, patients taking the wrong tablets or wrong strength of tablet/wrong dose, taking multiple doses, etc. This is potentially more problematic for patients on long term treatment who may receive several different generic products over time.

Another aspect that deserves consideration in this regard is that different colourings may be used either to attempt to match the colour of another formulation or to provide an entirely different colour. Although reasonably rare some patients can be allergic to one or more of the dyes/lakes/colourants used to produce the coloured product [62-64]. The variation in excipients used can be beneficial if it allows a patient to avoid those colours to which they react but could clearly be an issue if a change of generic leads them to be exposed to a colour which they do not tolerate even if the appearance is the same. Indeed, this may be a bigger risk if the appearance does not alert them to the fact that the colorants might have changed.

Although medicines are provided in labelled packaging, for some patients their medicines may be placed in multi-compartment compliance aids (MCAs). Changes in the appearance of medicines can be particularly confusing where they are separated from the packaging.

Similarity of these aspects among all versions of the same product might help avoid these issues and facilitate safer generic substitution.

Complexity of modification prior to administration

As a generic product can be different to the originator in terms of the formulation and even the pharmaceutical form, the ease of dose preparation prior to dosing (such as reconstitution or dispersion in water/food to aid administration) may be very different. As an example, a capsule may be easy to open for the content to be dispersed in water, whereas the tablet form might require crushing even if this is not allowed in the summary of product characteristics (SmPC). Although there are occasional instances where it is legitimate practice to crush tablets for this purpose (e.g. clobazam, L-cysteine, liothyronine) it may be more convenient to patients and carers to open a capsule than to crush a tablet. Similarly, a powder for reconstitution that requires more vigorous shaking could lead to a poorer patient experience or even dosing errors from undispersed material.

Sometimes it is necessary to dilute liquid preparations prior to administration via narrow enteral tubes e.g. to reduce viscosity. As generic versions can vary with regard to excipients it is possible that ease of administration via enteral tubes may vary between products. It is also possible that one might need dilution whilst another does not. Increased complexity is clearly more likely to result in error as well as being less acceptable to carers. The EMA has published guidance on instructions for enteral tube administration taking account the properties of the formulation [65].

Another example is where the innovator product or some generic versions are scored to aid dose adjustment but other versions are unscored or unlicensed for sub-division [66]. This may require unlicensed manipulations or the need for a specific makes of a medicine which can adversely affect generic substitution.

Required dose

It is possible that the costs of formulating and registering specific generic products for various paediatric patient groups are not commercially worthwhile. Unlike the case for the innovator, there is no compulsion for generic products to cater for all users and so generic manufacturers may simply choose not to seek authorisation for use of their products in certain sub groups or may delete indications for use in younger children if issues regarding suitability for use in these groups are raised. Some regulators have termed this "age-upping" and are concerned as the direction of travel should be increased availability of licensed medicines for all age ranges, especially the youngest.

As an example, given the relatively small market represented by neonates it is possible that generic manufacturers will not specifically develop formulations for all age groups but rather seek to adapt their adult or paediatric formulations for all age groups. Very small volumes of oral liquid medicines are sometimes required for neonates. Carers can struggle to measure such volumes. Even though official guidance provides help on minimum volumes to be measured with devices there is still the possibility that a specifically formulated product for neonates will be a different concentration to one adapted from an adult or paediatric formulation for a wider age range leading to different dose volumes. The smaller the dose volume, at least as a percentage of the overall volume of the dosing device (such as an oral syringe), the bigger the risk of dosing error—even if the dose is within "acceptable" limits. If the therapeutic index is narrow this could be even more problematic.

These differences in the age ranges of generic products compared to the innovator do not aid generic substitution. It may also dilute the economic benefit of using generics since it may be necessary to use one formulation (innovator) in some patient populations whilst being able to use another (generic) one in others complicating inventory requirements and costs in the pharmacy or increasing unintentional off-label use of some medicines.

Device

The "Guideline on pharmaceutical development of medicines for paediatric use" [17] states "unless otherwise justified liquid paediatric medicines should be supplied with a measuring device" and "the age appropriateness of an administration device should be discussed". There is also an EMA questions and answers (Q&A) document on gradations on oral liquid dosing devices [67]. However, there is no requirement for any administration device provided to be similar between formulations even of the same API. Clearly if the ease of use of the device supplied can both influence acceptability and dose accuracy. A proliferation of devices could lead to confusion and the wrong dose being administered.

Some respondents to our survey stated that the supply of measuring devices with products that are inaccurate or inappropriate for the age range/dose volume is a common assessment issue with generic applications as illustrated by the need for advice to applicants on this [67]. If the application is subsequently approved, it will be necessary for the manufacturer to have responded to this guidance to ensure that the eventual device supplied is appropriate. The costs involved may again mean that the manufacturer may choose not to pursue this indication.

In some hospital environments the issue of different devices being supplied may be somewhat mitigated by them choosing not to use the devices that come in packs and using their own bulk ones to avoid staff errors in picking a device. However, this has its own issues associated with dose measurement and dose accuracy as discussed in a recent seminar of the EuPFI on the topic [68].

Primary and secondary container closure system

Generic medicines are not required to be packaged in the same way as the innovator. Pack sizes, printing, colour, etc, may be different to the innovator. If the pack is less convenient for the user, then acceptability may be affected, especially if it is less portable. Conversely a generic manufacturer may be able to "spot a gap" in the market by providing packaging with enhanced functionality and thus provide their product with a competitive advantage. Differences in external packaging can lead to errors in product selection. The packaging design and style of generic medicines is usually not a copy of the original product (because of copyright and intellectual property rights) but is usually in accordance with the company-specific livery. Regulatory emphasis is on innovative pack design across manufacturers' product ranges which should ensure accurate identification of the individual products and differentiate between products in a range [69].

Importantly, if there is a risk of several pack types of the same medicine (for example a tub of tablets and a blister pack) being in the patient's home at the same time there could be a risk of both being taken leading to overdose. Manufacturers should therefore consider this risk when making decisions about how to package their products.

Constraints on Generic manufacturers

Whilst the forgoing discussion of various aspects of product development illustrates the potential risks of not considering acceptability as part of the approval of generic formulations (and hence the risk that this will not be high on the list of criteria being considered by the formulator), it has to be acknowledged that there are some constraints operating for the generic manufacturer, especially if the wish is to produce a product that is identical to the originator. The appearance, dosage device, and packaging of an innovator product may be protected by intellectual property rights that may outlive the patent protection for the API. There may also be risks associated with generics being passed off as the innovator product, although for reasons discussed earlier, it is unlikely for generic manufacturers to obtain exactly the same flavours, colours, excipient grades and so on. Exact copies of the innovator should not be necessary and perhaps in many cases not even desirable if there is an opportunity for the generic to have better acceptability than the originator.

There is also a cost involved in demonstrating that the generic product has acceptability that is at least not significantly worse than the originator, and this cost will need to be recouped by the developer. A "level playing field" in this aspect of the evaluation of all generic products by regulatory authorities is therefore required to ensure that manufacturers are not disadvantaged economically for developing products which are demonstrably acceptable to the patient. A slightly higher generic price for a product with good acceptability would avoid the economic risks associated with poorly acceptable generics, as discussed below.

Economic considerations and implications

The general assumption, and drive for generic prescribing in many countries is on the basis of saving costs for equal health gains [70]. From an economics perspective, the implicit approach when two products are therapeutically identical is one of cost-minimisation analysis, which has a decision rule of adopting the least costly option. However, as described in the foregoing, bio-equivalence (in the pharmacokinetic sense) may not necessarily translate to therapeutic equivalence (in the clinical sense) if there are differences in the characteristics of generic medicines that might impact patient preferences, introduce barriers to administration or lead to medication errors. These can each reduce adherence, limit effectiveness and cause harm. Consequently, a cost-minimisation framework is not appropriate where such differences exist. Likely differences in health outcomes, however small, dictate that cost-effectiveness (utility) analyses should be employed when assessing the value of generic products that are potentially not therapeutically equivalent [71].

Generic medicines are generally exempt from formal health technology assessment and appraisal in most jurisdictions. However, the Scottish Medicines Consortium (SMC) has a broad appraisal remit. In the case of hydrocortisone granules in capsules (Alkindi®), the SMC accepted that bioequivalence with hydrocortisone tablets had been established in clinical studies. The premise of the sponsor's economic analysis was for quality of life benefits and reduction in mortality from reduced risk of co-morbidity resulting from the ability of Alkindi® to deliver accurate and consistent dosing in young children [72]. In Germany this argument was not accepted [73] and as a result the statutory health insurance funds agreed on a reimbursement that is not as high as the manufacturer proposed, but higher than for that for the comparator product (tablet formulation or compounded capsule formulation).

The SMC accepted both mercaptopurine oral suspension (Xaluprine®) [74] and glycopyrronium bromide (Sialanar®) [75] for use by NHS Scotland without consideration of economic factors.

More generally in the UK, the prescribing of generic medicines is typically driven by pressure from commissioners and providers of medicines in their various guises (general practices, Clinical Commissioning Groups, etc.) to reduce costs. Formal economic evaluations are not conducted, and the consequences of this may lead to inefficiencies in the delivery of healthcare. Consider, for instance, a generic medicine which is significantly less expensive than the originator but, because of difference in appearance, is not adhered to by a proportion of patients. These patients may experience a recurrence of symptoms, impairment of quality of life etc, depending on the disease being managed. If worsening of symptoms were to lead to hospital attendance, additional test etc, then the savings would soon evaporate, and costs could increase overall [20]. While this may be somewhat theoretical, with little direct evidence, it is nonetheless plausible, especially as the cost of hospitalisation and associated care considerably exceeds the likely savings, even if this is a rare occurrence [76].

Conclusion

As we have demonstrated in this paper a lack of consideration of the acceptability of the generic product could undermine treatment efficacy and safety in certain populations, and thereby reduce the potential considerable cost saving that could be achieved by promoting the use of generic medicines. Failure to produce a generic that is acceptable to the patient and their caregiver can not only lead to potential for treatment failure *via* non concordance with therapy but potentially also significant extra costs. Thus, ensuring substantial cost savings by promoting use of generic products

requires equality in term of not only quality, safety and efficacy in clinical studies, but also acceptability and hence efficacy in use.

Given the current International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) focus on unifying guidance on the development and scrutiny of generics [77] it is very timely to state our position on this topic [78] and to seek to influence the growing debate to ensure that acceptability is included alongside the other factors being considered for harmonization.

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Reference number	Article	Category	Medication	Population	Method	Key findings
39	Bagger-Sjoback D., et al. 1989. Taste evaluation and compliance of two paediatric formulations of phenoxymethylpenicillin in children. Scand J Prim Health Care. 7:87-92.	Drugs Evaluation	2 penicillin suspensions	Children 3–10 years with otitis media	Child's spontaneous verbal judgment and parent's judgment of acceptability.	No differences in taste scores between two suspensions.
33	Baguley D., et al. 2012. Prescribing for children - taste and palatability affect adherence to antibiotics: a review. Arch Dis Child. 97(3): 293-7.	Review	Antibiotics	Paediatric	Reviewing the clinical evidence around palatability of antibiotics.	Certain drugs, for example flucloxacillin, are so unpalatable that they should not be prescribed as syrups without prior 'taste testing' in an individual child, while others, such as oral cephalosporins, are accepted very well although they are more expensive with a broader antimicrobial spectrum than may be strictly necessary.
21	Belissa E., et al. 2019. Acceptability of oral liquid pharmaceutical products in older adults: palatability and swallowability issues. BMC Geriatrics. 19(1), 1-9.	Drugs Evaluation	Oral liquid pharmaceutical products	Elderly	Explorations were performed using the CAST - ClinSearch Acceptability Score Test®.	Oral liquid pharmaceutical products are a suboptimal alternative to solid oral dosage forms in patients with swallowing disorders. Palatability remains crucial in older populations, especially for women.
29	Cohen R., et al. 2009. Study of the acceptability of antibiotic syrups, suspensions, and oral solutions prescribed to pediatric outpatients. Eur J Pediatr. 168(7):851-7.	Drugs Evaluation	3 antibiotic syrups, suspensions, and oral solutions most often prescribed to children in France: amoxicillin–clavulanic acid (princeps and generics), amoxicillin (princeps and generics) and cefpodoxime proxetil (princeps as no generics were available)	953 children from 0.5 months to 14 years to whom a pediatrician had prescribed an antibiotic in the form of a syrup, suspension, or oral solution	Taste assessment based on representations of five facial expressions.	Differences in palatability and acceptability between amoxicillin–clavulanic acid reference products and some generics. Such differences do not appear between amoxicillin reference products and amoxicillin generics.
not discussed [only abstract, full article not found]	Demers D.M., et al. 1994. Antimicrobial drug suspensions: a blinded comparison of taste of twelve common pediatric drugs including cefixime, cefpodoxime, cefprozil and loracarbef. Pediatr Infect Dis J. 13(2):87-9.	Drugs Evaluation	12 antimicrobial suspensions including Lorabid, Keflex, Suprax, Cefzil, Augmentin, Vantin, Ceclor, Sulfatrim, Pediazole, Dynapen, V-Cillin-K, Veetids and two penicillin VK suspensions	Paediatric	Smell, texture, taste, aftertaste and overall acceptance.	No difference overall was detected between the two penicillin VK suspensions evaluated.
47	Desai R.J., et al. 2018. Differences in rates of switchbacks after switching from branded to authorized generic and branded to generic drug products: cohort study. BMJ. 3;361:k1180.	Cohort Study	Branded products and authorized generics (same active ingredients, appearance, and excipients as the branded product) or generic drug products (same active ingredients as the branded product but may differ in appearance and excipients) for one of the study drugs: alendronate tablets, amlodipine tablets, amlodipine-benazepril capsules, calcitonin salmon nasal spray, escitalopram tablets, glipizide extended release tablets, quinapril tablets, and sertraline tablets.	94 909 patients switched from branded to authorized generic drug products and 116 017 patients switched from branded to generic drug products	Switchbacks to the branded drug product in the year after their switch to an authorized generic or a generic drug product.	Switching from branded to authorized generic drug products was associated with lower switchback rates compared with switching from branded to generic drug products.
10	El-Chaar G.M., et al. 1996. Randomized, double blind comparison of brand and generic antibiotic suspensions: II. A study of taste and compliance in children. Pediatr Infect Dis J. 15:18-22.	Drugs Evaluation	Brand and generic antibiotic suspensions of cephalexin, erythromycinsulfisoxazole and trimethoprimsulfamethoxazole approved in the US	Children 3–14 years with clinical indication	Patient's verbal response and facial hedonic scale to rate taste and aftertaste, and parent's rating of ease of administering medication.	For cephalexin, and for erythromycin-sulfisoxazole: no significant differences between generic products and the innovator in terms of taste and compliance. For trimethoprim-sulfamethoxazole, the innovator tasted better than the generic product, but there was no difference in compliance.
not discussed [no focus on drugs]	Figueiras M.J., et al. 2009. Assessing lay beliefs about generic medicines: Development of the generic medicines scale. Psychol Health Med. 14(3):311-21.	Tool development	Generic medicines	228 Portuguese pilot study (Stage I) 819 Portuguese main study (Stage II)	Development of the generic medicines scale (GMS) Stage I: item generation and pilot study Stage II: main study	Two-factor structure concerning beliefs about generic medicines, comprising two core themes: efficacy and similarity to brand medicines.
31	Gauzit R., et al. 2012. Generic antibiotic drugs: is effectiveness guaranteed? Médecine et maladies infectieuses. 42(4):141-148.	Review	Generic antibiotic drugs	-	-	There is a specific problem of taste and treatment acceptability for pediatric oral antibiotic drugs. It seems necessary to review regulations for marketing authorization of generic antibiotic drugs.
36	Inoue Y., et al. 2012. Study of the physicochemical properties of tulobuterol dry syrups using taste and smell sensors. Chem Pharm Bull (Tokyo). 60(4):442-8.	Drugs Evaluation	Tulobuterol Dry Syrup in its original form and 2 generic forms	25 healthy well-trained human volunteers with an average age of 23 years	Gustatory sensation tests, taste and smell sensors, and physicochemical properties measurement.	Differences in preparations were presumably caused by variations in manufacturing specifications, such as types of additives and their content and coating methods used.
not discussed [Informal taste test]	Ito M.K., et al. 1999. A matter of taste. Am J Health Syst Pharm. 56(1):80-1.	Drugs Evaluation	2 bile acid sequestrants mixtures: Prevalite (generic) and Questran Light (innovator)	10 tasters from pharmacy administrative personnel at health system	Informal taste test: 5-point scale for taste, texture and smell.	Tasters preferred Questran Light over Prevalite for taste, smell and overall quality.
27	Jahnsen T., et al. 1987. An acceptability study of two pivampicillin mixtures in children in general practice. Scand J Prim Health Care. 5:241-243.	Drugs Evaluation	2 pivampicillin mixtures	Children 1–7 years with infection	Child's evaluation of taste or parent's evaluation of administration.	Better acceptability and easier administration with banana than cocoa-peppermint taste.
not discussed [only abstract, full article in Polish]	Kardas P., et al. 2005. [A blinded comparison of palatability of 13 common pediatric antibiotic suspensions]. Wiad Lek. 58(1-2):15-20.	Drugs Evaluation	13 antibiotic suspensions	25 volunteers	Appearance, smell, texture, taste and aftertaste compared to amoxycillin (Amotaks) as a reference drug.	In overall score, different preparations of the same substance obtained similar scores, statistically non-different, with one exception for clarithromycin, in which Klacid was characterized by better palatability.
34	Kim M.K., et al. 2006. Vomiting of liquid corticosteroids in children with asthma. Pediatr Emerg Care. 22:397-401.	Drugs Evaluation	2 prednisolone liquid preparations	Children 2–10 years with acute asthma exacerbation	Five point facial hedonic scale (>5 years of age).	Better taste score for Orapred than generic prednisolone.
not discussed [ocular formulations in adults]	Kim Y.I., et al. 2015. Efficacy and Safety of Glaucoma Patients' Switch from a 2% Dorzolamide/0.5% Timolol Fixed-Combination Brand-Name Drug to Its Generic Counterpart. J Ocul Pharmacol Ther.31(6):335-9.	Drugs Evaluation	2 eye drops: brand-name and generic of 2% dorzolamide/0.5% timolol fixed-combination drugs (DTFC)	112 patients with a mean age of ≈ 63 years	Questionnaire on discomfort symptoms and on discomfort score for the use of eye drops.	There were higher incidences of bitter taste and blurring with Cosopt (brand-name), and there was a higher incidence of headache with Batidor (generic), but no significant differences ($P > 0.05$) were noted. There was, likewise, no significant difference in the discomfort score between 2 drugs.
40	Kraus M., et al. 2001. Effectiveness and Infant Acceptance of the Rx Medibottle versus the Oral Syringe. Pharmacotherapy. 21(4):416–423.	Device Evaluation	Acetaminophen (Tempra syrup) delivered by the Rx medibottle or with an oral syringe	30 healthy, bottle-fed infants, aged 2–14 months, receiving routine vaccinations	Effectiveness was based on the percentage of infants receiving 100% of the intended dose. Infant acceptance was scored using a validated infant medication acceptance scale (MAS).	Significantly more infants received 100% of the intended dose with the Rx medibottle (93.3%) than with the oral syringe (56.7%, p=0.0074). Infants had a significantly higher mean MAS score when using the Rx medibottle (8.3 ± 1.8 vs 7.3 ± 1.7, p=0.002). A significantly higher percentage had ideal MAS scores of 9 or above with the Rx medibottle (73%) compared with the oral syringe (17%, p=0.0001).
not discussed [only abstract, full article in Japanese]	Matsuo R., et al. 2008. [Bitterness of the mixture of clarithromycin dry syrup and carbocisteine preparation--difference between brand name and generic drugs]. Yakugaku Zasshi. 128(3):479-85.	Drugs Evaluation	Mixture of clarithromycin dry syrup and carbocisteine preparation: brand name and generic	6 healthy male volunteers	Human gustatory sensation tests.	The extent of bitterness of the mixture of clarithromycin dry syrup and carbocisteine preparation highly varies among the generic formulations.
not discussed [only abstract, full article in Japanese]	Miura Y., et al. 2007. [Sensory evaluation test: odor component analysis and endotoxin content of Krestin and Carbocrin (generic drug) to compare palatability]. Gan To Kagaku Ryoho. 34(8):1259-63.	Drugs Evaluation	Krestin and Carbocrin (generic drugs)	No information	Sensory evaluation test. Questions were asked on the odor, taste, feeling on the tongue, and overall evaluation, to find out which is easier to swallow.	Krestin is significantly superior to Carbocrin, showing a clear difference in palatability between the two products.

46	Riner B., et al. 2017. "No generics, Doctor!" The perspective of general practitioners in two French regions. BMC Health Serv Res. 17(1):707.	Survey	Generic medicines	316 General practitioners from Marinique & Guadeloupe	Survey	The main reported disadvantage concerned "Patients may be confused by changes in presentation" (47% of the questioned practitioners), then "Presentation and dosage form differ between laboratories for the same molecule" (44% of the questioned practitioners). They were caught between the requirements of health insurance regimes and the opposition of numerous users and suggested that the patient information provided by health authorities should be improved and that drug composition and packaging should be made uniform. One of the simplest solutions to make generics more acceptable to both prescribers and patients could be uniformization of their presentations by delivering exact copies (same active and inactive ingredients) or the same generic product to the same patient for a given originator product.
6	Ruiz F., et al. 2019. Sex Differences in Medicine Acceptability: A New Factor to Be Considered in Medicine Formulation. Pharmaceutics. 11(8):368	Drugs Evaluation	2 original formulations of memantine: tablets and oral solution	Elderly	Evaluations were scored with the acceptability reference framework (CAST - ClinSearch Acceptability Score Test®) and the rodent Brief Access Taste Aversion (BATA) model tested aversiveness.	Acceptability issues with the original oral solution of memantine driven by palatability. According to CAST the coated tablet, which created a physical barrier between the memantine hydrochloride and taste buds, was well accepted in the older population, while this appeared not to be the case for the oral solution. The BATA model objectively confirmed the aversiveness of this formulation. Exploring sex differences, consistent findings from both human studies and animal models highlighted a higher sensitivity of the females to this unpalatable oral formulation as the proposed cause for suboptimal acceptability.
9	Samulak K.M., et al. 1996. Randomized, double blind comparison of brand and generic antibiotic suspensions: I. A study of taste in adults. Pediatr Infect Dis J. 15(1):14-17.	Drugs Evaluation	Generic products of cephalexin, erythromycin ethylsuccinatesulfisoxazole, penicillin V, and trimethoprimsulfamethoxazole approved in the US	42 adult volunteers	Subjects tasted one class of brand and generic antibiotics and rated them according to smell, texture, taste and aftertaste.	At least one generic preparation of cephalexin, erythromycin ethylsuccinate/sulfisoxazole and penicillin V potassium was rated equal in taste to the respective brand name products. However, brand erythromycin estolate and trimethoprim-sulfamethoxazole name brand suspensions rated significantly higher than the other products tested. For cephalexin, penicillin V and erythromycin ethylsuccinate/sulfisoxazole: the taste of generic products was rated equal to that of the innovators. For trimethoprim-sulfamethoxazole and erythromycin estolate, the taste of the innovators was rated higher than that of the generic products
25	Sjövall J., et al. 1984. Methods for evaluating the taste of paediatric formulations in children: A comparison between the facial hedonic method and the patients' own spontaneous verbal judgement. European journal of pediatrics. 141(4):243-247.	Drugs Evaluation	3 oral suspensions of bacampicillin. 2 penicillin syrups were included as reference drugs, formulation W assumed to be pleasant to the taste and formulation U assumed to have an unacceptable taste on the basis of clinical experience.	103 children with upper respiratory tract infections - 3-12 years of age - with signs of bacterial infection for which treatment with penicillin was indicated	Patient's own spontaneous verbal judgement and hedonic scale of facial expressions.	Formulation W must be considered the most liked one, while the U and C formulations were liked the least. The A and B formulations were ranked in between.
28	Stevens R, et al. 1996. A randomized study of ondansetron syrup in children: evaluation of taste acceptability and tolerance. Pediatr Hematol Oncol. 13:199-202.	Drugs Evaluation	2 flavours of ondansetron syrup	Children 3–12 years undergoing chemotherapy	Panel of five faces and asked preference.	Preference for strawberry formulation
32	Tattevin P., et al. 2013. Efficacy and quality of antibacterial generic products approved for human use: a systematic review. Clinical infectious diseases. 58(4):458-469.	Review	Generic medicines	-	Search on Medline and Embase for original research articles on antibacterial generic products published in English or French before July 2013.	Of the 37 studies, 14 (37.8%) suggested that some generic products may be inferior to the innovator in terms of purity (n=2), in vitro activity (n=3), in vivo efficacy in experimental models (n=4), clinical efficacy (n=2), taste (n=2), or compliance and acceptability in children (n=1).
37	Tokuyama E., et al. 2009. Famotidine Orally Disintegrating Tablets: Bitterness Comparison of Original and Generic Products. Chemical and Pharmaceutical Bulletin. 57(4):382-387.	Drugs Evaluation	9 formulations of famotidine orally disintegrating tablets: the original manufacturer's formulation and eight generic versions	11 well-trained volunteers	Human gustatory sensation tests, a comparison of the release profiles, and taste sensor measurements.	The bitterness intensities of the generic products A, E and F showed significantly stronger bitterness compared with the original product, while no significant differences in sweetness scores were found between the original and the generic products, which was significantly less sweet than the original product. Among the eight generic products tested, the variance in the sweetness intensity was not great, but there were large variances in the intensity of bitterness, some of the generic products being significantly more bitter than that of the original product. On the other hand, some generic products show similar bitterness level as the original product.
45	Toverud E.L., et al. 2011. Norwegian patients on generic antihypertensive drugs: a qualitative study of their own experiences. Eur J Clin Pharmacol. 67(1):33-8.	Survey	Generic antihypertensive drugs	22 patients from pharmacies in Oslo who had taken brand antihypertensive products as well as substituted generic products	Focus-group discussions.	Most reported low drug adherence before and after generic substitution. Differences in name, color, form, or taste caused confusion.
41	U.S. Department of Health and Human Services. Food and Drug Administration. 2015. Size, shape, and other physical attributes of generic tablets and capsules guidance for industry. Fed. Regist.:35366–35367	Guidance	Generic tablets and capsules	-	-	Differences in physical characteristics (e.g., size and shape of the tablet or capsule) may affect patient compliance and acceptability of medication regimens or could lead to medication errors.
38	Uchida T., et al. 2013. Evaluation of palatability of 10 commercial amlodipine orally disintegrating tablets by gustatory sensation testing, OD-mate as a new disintegration apparatus and the artificial taste sensor. Journal of Pharmacy and Pharmacology. 65(9):1312-1320.	Drugs Evaluation	10 formulations of amlodipine orally disintegrating tablets: the original manufacturer's formulation and nine generic versions	6 healthy female subjects, 26 +/- 9 years old	Human gustatory sensation testing (bitterness intensity, disintegration time in the mouth, palatability in the mouth and after splitting out), disintegration/dissolution testing, and the evaluation of bitterness intensity using a taste sensor.	The factors most affecting the palatability of amlodipine ODTs were found to be disintegration and taste.
not discussed [proxy measure]	Uestuener P., et al. 2014. Taste acceptability of pulverized brand-name and generic drugs containing amlodipine or candesartan. Int J Pharm. 468(1-2):196-8.	Drugs Evaluation	the brand-name and the most prescribed generic medicines containing either amlodipine, a popular calcium-channel blocker with a bitter taste, or candesartan, a recognized angiotensin type 2 receptor antagonist	healthy health care workers: 19 nurses and 12 physicians aged between 25 and 49 years.	A smiley-face scale depicting four degrees of pleasure.	Pulverized brand-names and generics containing either amlodipine or candesartan did not differ with respect to their taste acceptability.
26	Uhari M., et al. 1986. Acceptance of Antibiotic Mixtures by Infants and Children. Eur J Clin Pharmacol. 30:503-504.	Drugs Evaluation	containing either amlodipine, a popular calcium-channel blocker	76 patients range 0.2 to 8.1 years	The time a nurse required to give the drug to a child was recorded and a score of the acceptance was given by the nurse.	The time difference was significantbetween erythromycin Brand 1 and 2, while the difference between the two penicillin products was not significant.
35	Woertz K., et al. 2011. Development of a taste-masked generic ibuprofen suspension: top-down approach guided by electronic tongue measurements. J Pharm Sci. 100(10):4460-70.	Drugs Evaluation	with a bitter taste, or candesartan, a recognized angiotensin type 2	-	Electronic Tongue Measurements.	The results from the electronic tongue measurements clearly showed that the formulations could be distinguished according to their excipients and manufacturer.
30	Wollner A., et al. 2011. Acceptability, compliance and schedule of administration of oral antibiotics in outpatient children. Archives de pediatrie: organe officiel de la Societe francaise de pediatrie. 18(5):611-616.	Drugs Evaluation	receptor antagonist	1482 patients < 6 years	Taste assessment based on representations of five facial expressions.	This study confirms the disparity in terms of acceptability among the different antibiotics prescribed for children even for the same drug, warranting evaluation for marketing of future generic drugs pediatric oral suspension.

Table 2 - Survey key findings

Do some formal or informal discussions take place regarding acceptability of generic vs originator medicines?		
Yes	**Croatia**	*If generic differs from reference in any characteristics, it would be explained and justified in a medicinal product dossier. The dossier is then assessed by competent authorities during the marketing authorisation procedure.*
	Netherlands	*For paediatric products, age-appropriateness of the formulation will be considered in the assessment of the product (as well as when comparing to the original).*
In some cases	**Denmark**	*Generic application does not require evaluation of acceptability. Only one application where palatability was tested in adults.*
	Estonia	*Deviations from the originator will be discussed during the assessment of the marketing authorisation application.*
	Greece	*Not much detail in the email.*
	Ireland	*Considers appropriateness of various forms of medication for certain patient groups. However, they do not have a formal standard operating procedure (SOP) for this.*
	Latvia	*Issues will usually be discussed in EU member state delegate meetings.*
	Slovakia	*Some discussion regarding acceptability took place around 10 years ago when generic prescription was legalized.*
	Slovenia	*Not really answered in the email. The Agency for Medicinal Products and Medical Devices of the Republic of Slovenia (JAZMP) decides on the acceptability of Medicinal Products on the bases of positive risk/benefit ratio which is derived from the scientific Assessment Report prepared by the experts on the submitted documentation of given Medicinal Product. This also applies for generic Medicinal Products. In the European mutual recognition procedure (MRP) and decentralised procedure (DCP) marketing authorisations are granted on bases of Assessment Reports prepared by the Reference Member State (RMS).*
	UK	*Assessment of paediatric medicines would take into account current regulatory guidance, most notably the EMA guideline "Pharmaceutical development of medicines for paediatric use" [12]. For adults, there is currently no requirement for generic versions of solid dosage forms to be the same size or shape as the originator. These aspects may nonetheless be considered during assessment where required.*
No	**Belgium**	
	Iceland	
	Spain	
	Sweden	*There is a formal review system after approval of generic product; they will evaluate the suitability of the product to be substituted at the pharmacy level with certain criteria.*